

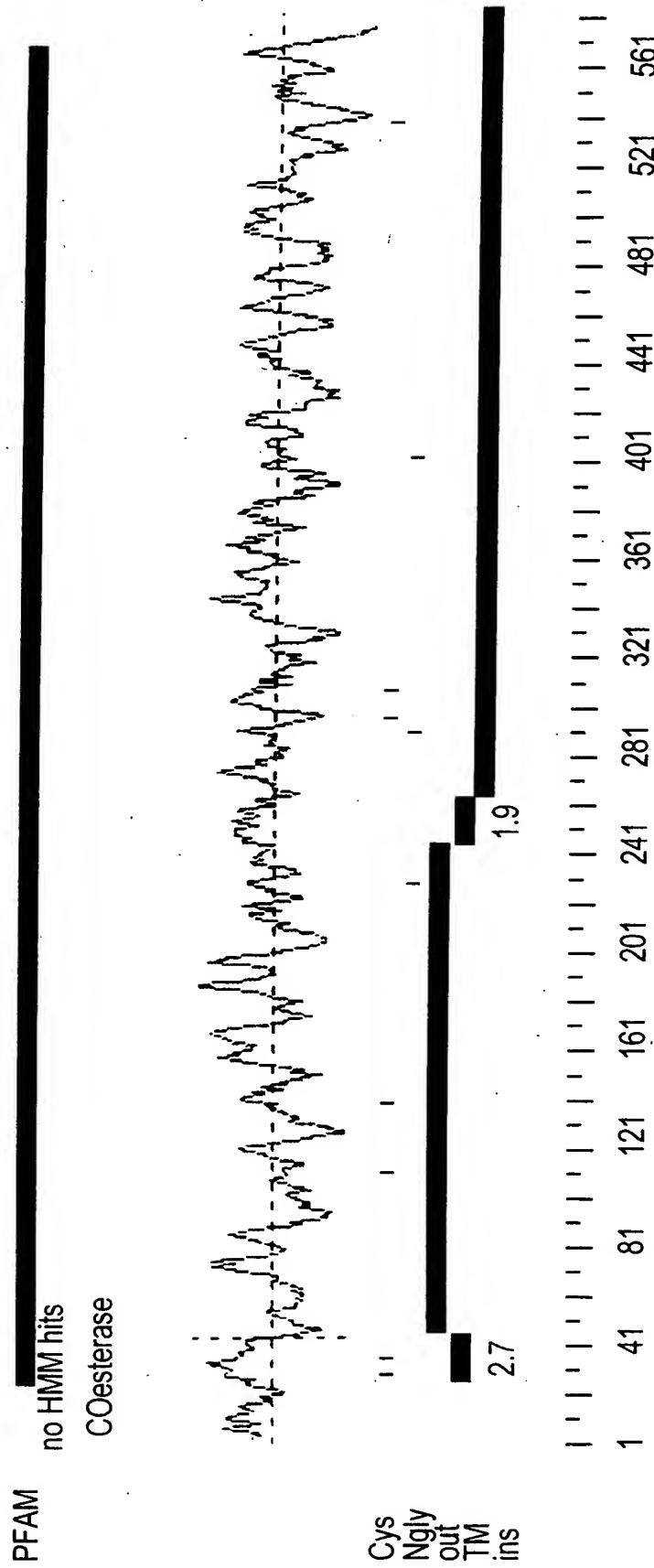


REPLACEMENT SHEET

Applicant: Rosana Kapeller-Libermann, et al.
Title: METHODS OF USING 18903 TO TREAT PAIN AND PAIN-RELATED
DISORDERS
Application No.: 10/001,227
Attorney/Agent: Mario Cloutier
Docket No.: MPI00-408P1RM

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FIG. 1





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FIG. 2A

Protein Family / Domain Matches, HMMer version 2

Searching for complete domains in PFAM
 hmmpfam - search a single seq against HMM database

HMMER 2.1.1 (Dec 1998)

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 HMMER is freely distributed under the GNU General Public License (GPL).

HMM file: /prod/ddm/seqanal/PFAM/pfam6.4/Pfam
 Sequence file: /prod/ddm/wspace/orfanal/oa-script.6214.seq

Query: Fbh18903FL

Scores for sequence family classification (score includes all domains):

Model	Description	Score	E-value	N
Coesterase	Carboxylesterase	558.6	4.1e-164	1

Parsed for domains:

Model	Domain	seq-f	seq-t	hmm-f	hmm-t	score	E-value
Coesterase	1/1	25	569 ..	1	612 []	558.6	4.1e-164

Alignments of top-scoring domains:

Coesterase: domain 1 of 1, from 25 to 569: score 558.6, E = 4.1e-164
 *->mvllllflllllliavllaaakaspedpl1VatnnV1cGkvrgvnek

+1+ +L 1 1 ++ +1+a++ ++ V t++ ++ G++ G++
 18903 25 RWILCWSLTLCLMAQTAIGALHT---KRPQVVVTRY---GTLQGKQMH 65

tdngeqsvsysF1G1PYAePPVGnLRFkaPqPYkePwsdvl1dAtkyppsc1
 + ++ +F1G+P+ PP+G LRF +P+P +epW+++dAt+YPP C1
 18903 66 VCGKT--PIQVFLGVPPFSRPPPIGLRFAPPEP-PEPWKGIRDAATTYPPGCL 112



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FIG. 2B

18903	113	QdddfgfsldIKvalkmlsIgwnkIvg...1klEDCLYLNVytPknt Q + +g+ 1 +++ ++ + + 1 + +EDCLYLNV P+ + Q-ESWGQ-----LASMVSTRERYkwIRFSEDCLYLNVYAPARA 150
18903	151	kpnsklPVmVwIhGGGFmfgsghs1plslYdgeslaregnV1vVsINyRL + + 1PvVw +GG+F +G++ s+Y g+ 1at++V++V ++ RL PGDPQLPVMWFGGAIFIYGA-----SSYEGSDLAAAREKVVLFQHRL 195
18903	196	GpIGFLstgddk1pgsGNYGL1DQrlALKwVqdnN1aaFGGDPnsVTifGe G++GFLst+d++ GN+GL1DQ +AL+wVq+NIaafGDDP++VT+FG+ GIFGFLSTDDSHAR--GNWGL1DQMAALRWQENIAAFGGDPGNVTLFGQ 243
18903	244	SAGaaSVslllsngGDNppsskgIFlHRAIsqSGsalspwaiqsesnarg SAGa+S+s 1+s p+ gLFHRAIsqSG+al +i+s+ + SAGAMSISGIMMS-----PLA-SGLFHRRAISQSGTALFRLFITSNP--LK 285
18903	286	rakelar11GChnetssselldCLRsksaeeLleatrsfllfeyvpf1plf ak+a 1+GCn+s 1+ CLR s + + + f + +f + VAKKVAHLAGCNHNSTQILVNCRLALS GTKVMRVSNK-MRFQLQNFQRD P 334
18903	335	1...aFgPvvDGDaapeafipedPeelikeGkfadvPyliGvtkdeGqy ++ + +PvvDG+ +ip+dp+ 1+ +Gk + vPy1 Gv++ E+ + EeiwSMSPVVDGV-----VIPDDPLVLLTQGKVSSPVLLGVNNNLEFNW 379
18903	380	faamllnasskgdedelkkketnpdwlellkyllfyasealn1kdmddlad ++++ + + ket ++ 1+ 11+ + + + LIPYIMKRFPLNR-QAMRKETITK-MIWSRTLLN-ITKEQ-----VP 418
18903	419	krlekXpgdvdffsvesrkpn1qdm1td11Fkcptrvaad1hakhqgsPv v e+Y++ v + + ++ d++ D +F++ + ++ ++++g Pv LVVEEYLDNVNEHDWKMRLRNRMMDIVQDATEVYA-TLQTAHYHRDAGLPV 467



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FIG. 2C

18903	468	YLYEEFHAR-----GIIVKPRTDGADHGDEMFLFGGPFATG-LS-- 507	YaYvf dhpasfgigQflakrvdpesfggavHgdeiffvFgnplllkeqlyka Y+Y+f h+a+ + v+p+++ga+Hgde++f+fg p+ ++ 1
18903	508	MGKEKALS-LQMMKYWANFARTGNP-NDG--NLPcwPRYNKDEK--YLQL 51	teeekssk tmmnywanFAktGnPnngtsng1vvwpkytseeqkyslli e++s +mm+ywanaFA+tGnP n++ +1+ wp y++e +1+
18903	552	DFTTRVGMKLKEKK-----MAFW 569	1lttitaqk1kardpdkv1cnfw<-* +tt +k1k++ ++fw

// Searching for complete domains in SMART



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FIG. 3A

GAP of: FrGcgManager_76_IOA81nWg_ check: 5132 from: 1 to: 1983

Fbh18903FL - Import - vector trimmed

to: FrGcgManager_76_JOA3WXZ1_ check: 1319 from: 1 to: 2456

z34105 in Patent Nucleotide

Symbol comparison table: /ddm_local/gcg/gcg_9.1/
 1/gcgcore/data/rundata/nwsgapdna.cmp
 CompCheck: 8760

Gap Weight:	12	Average Match:	10.000
Length Weight:	4	Average Mismatch:	0.000
Quality:	13796	Length:	2746
Ratio:	6.957	Gaps:	14
Percent Similarity:	92.617	Percent Identity:	92.617

Match display thresholds for the alignment(s):

| = IDENTITY
 : = 5
 . = 1

FrGcgManager_76_IOA81nWg_ x FrGcgManager_76_JOA3WXZ1

COE-2 1 CCT 3

z34105 101 CATTTCGCCTTGCTGACGGCGTCGAGCCCTGGCCAGACATGTCCACAGGG 150

4 TTAGCCAATT CGGCCGAGGCTCCGCCAGTA. CTTGCTGGCAGGGAT 52

151 TTCTCCTTCGGGTCCGGGACTCTGGCTCCACCACCGTGGCGCCGGCGG 200

53 TAAGAGCAGA. TAAAAGTGTGCTCACACACTGTAGACACGGCTACCATGC 101

201 GACCAGCACAGGCGCGTTCTCCTCGGAACGGGAACGTCTAGCAACC 250

102 CATC. CACAGTGTGCCATCCACAGTGTGCTACACTCCTGC. 143

251 CTTCTGTGGGGCTCAATTGGAAATCTGGAAGTACTTCAACTCCAGCA 300

144 .CCACAGCAGGAGCT..GGCTGGAGCATGAGGTGGATTCTGTG..CTGGA 188

301 ACTACATCTGCTCCTCAAGTGGTTGGAACCGGGCTCTTGGATCTAA 350



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FIG. 3B

189 GCCTCACCCCT...CTGCCTGATGGCGCAGACGGCCTGGGTGCCTGCAC 235
351 ACCTGCCACTGGGTTCACTCTAGGAGGA.ACATAACAGGTGCCTGCAC 399
236 ACCAAGAGGCCTCAAGTGGTCACCAAATGGAACCCCTGCAAGGAAAACA 285
400 ACCAAGAGGCCTCAAGTGGTCACCAAATGGAACCCCTGCAAGGAAAACA 449
286 GATGCATGTGGGAAGACACCCATCCAAGTCTTTAGGAGTCCCCTCT 335
450 GATGCATGTGGGAAGACACCCATCCAAGTCTTTAGGAGTCCCCTCT 499
336 CCAGACCTCCTCTAGGTATCCTCAGGTTGCACCTCCAGAACCCCCGGAG 385
500 CCAGACCTCCTCTAGGTATCCTCAGGTTGCACCTCCAGAACCCCCGGAG 549
386 CCCTGGAAAGGAATCAGAGATGCTACCACTACCCGCCTG..... 425
550 CCCTGGAAAGGAATCAGAGATGCTACCACTACCCGCCTGGATGGAGTCT 599
426GGTGCCTGCAGGAGTCCTGGGCCAGCTGGCCTCGATGTA 465
700 TGGGGCTACAGGTGCCTGCAGGAGTCCTGGGCCAGCTGGCCTCGATGTA 749
466 CGTCAGCACGCGGGAACGGTACAAGTGGCTGCGCTCAGCGAGGACTGTC 515
750 CGTCAGCACGCGGGAACGGTACAAGTGGCTGCGCTCAGCGAGGACTGTC 799
516 TGTACCTGAACGTGTACGCGCCGGCGCGCGCCCCGGGATCCCCAGCTG 565
800 TGTACCTGAACGTGTACGCGCCGGCGCGCGCCCCGGGATCCCCAGCTG 849
566 CCAGTGATGGTCTGGTCCCGGGAGGCGCCTTCATCGTGGCGCTGCTTC 615
850 CCAGTGATGGTCTGGTCCCGGGAGGCGCCTTCATCGTGGCGCTGCTTC 899
616 TTCTGACGAGGGCTCTGACTTGGCCGCCCGCGAGAAAGTGGTGTGGTGT 665
900 TTCTGACGAGGGCTCTGACTTGGCCGCCCGCGAGAAAGTGGTGTGGTGT 949
666 TTCTGACGACAGGCTCGGCATCTCGGCTCCTGAGCACGGACGACAGC 715
950 TTCTGACGACAGGCTCGGCATCTCGGCTCCTGAGCACGGACGACAGC 999
716 CACGCGCGCGGGAACTGGGGCTGCTGGACCAGATGGCGGCTCTGCGCTG 765



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FIG. 3C

766	GGTGCAGGAGAACATCGCAGCCTCGGGGGAGACCCAGGAAATGTGACCC	815
1050	GGTGCAGGAGAACATCGCAGCCTCGGGGGAGACCCAGGAAATGTGACCC	1099
816	TGTCGGCCAGTCGGCGGGGCCATGAGCATCTCAGGACTGATGATGTCA	865
1100	TGTCGGCCAGTCGGCGGGGCCATGAGCATCTCAGGACTGATGATGTCA	1149
866	CCCCTAGCCTCGGGTCTCTTCATCGGGCCATTCCCAGAGTGGCACCGC	915
1150	CCCCTAGCCTCGGGTCTCTTCATCGGGCCATTCCCAGAGTGGCACCGC	1199
916	GTTATTCAGACTTTCATCACTAGTAACCCACTGAAAGTGGCCAAGAAGG	965
1200	GTTATTCAGACTTTCATCACTAGTAACCCACTGAAAGTGGCCAAGAAGG	1249
966	TTGCCACCTGGCTGGATGCAACCACAACAGCACACAGATCCTGGTAAAC	1015
1250	TTGCCACCTGGCTGGATGCAACCACAACAGCACACAGATCCTGGTAAAC	1299
1016	TGCCTGAGGGCACTATCAGGGACCAAGGTGATGCGTGTGTCACAAGAT	1065
1300	TGCCTGAGGGCACTATCAGGGACCAAGGTGATGCGTGTGTCACAAGAT	1349
1066	GAGATTCCACTGAACCTCCAGAGAGACCCGGAAGAGATTATCTGGT	1115
1350	GAGATTCCACTGAACCTCCAGAGAGACCCGGAAGAGATTATCTGGT	1399
1116	CCATGAGCCCTGTGGTGGATGGTGTGGTATCCCAGATGACCCCTTGGT	1165
1400	CCATGAGCCCTGTGGTGGATGGTGTGGTATCCCAGATGACCCCTTGGT	1449
1166	CTCCTGACCCAGGGGAAGGTTCATCTGTGCCCTACCTTAGGTGTCAA	1215
1450	CTCCTGACCCAGGGGAAGGTTCATCTGTGCCCTACCTTAGGTGTCAA	1499
1216	CAACCTGGAATTCAATTGGCTTTGCCTTATATCATGAAGTTCCCGCTAA	1265
1500	CAACCTGGAATTCAATTGGCTTTGCCTTAT.....	1530
1316	CGCACCCCTGTTGAATATCACCAAGGAGCAGGTACCACTTGTGGTGGAGGA	1365
1531AATATCACCAAGGAGCAGGTACCACTTGTGGTGGAGGA	1568
1366	GTACCTGGACAATGTCAATGAGCATGACTGGAAGATGCTACGAAACCGTA	1415

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FIG. 3D

1416 TGATGGACATAGTTCAAGATGCCACTTCGTGTATGCCACACTGCAGACT 1465
 |||||||
 1619 TGATGGACATAGTTCAAGATGCCACTTCGTGTATGCCACACTGCAGACT 1668
 |||||||
 1466 GCTCACTACCACCGAGATGCCGGCCTCCCTGTCTACCTGTATGAATTGA 1515
 |||||||
 1669 GCTCACTACCACCGA..... 1683
 .
 .
 .
 1666 CAACTTGCCTGCACAGGAAACCCAATGATGGGAATCTGCCCTGCTGGC 1715
 |||||||
 1684GAAACCCAATGATGGGAATCTGCCCTGCTGGC 1716
 |||||||
 1716 CACGCTACAACAAGGATGAAAAGTACCTGCAGCTGGATTTACCAAGA 1765
 |||||||
 1717 CACGCTACAACAAGGATGAAAAGTACCTGCAGCTGGATTTACCAAGA 1766
 |||||||
 1766 GTGGGCATGAAGCTCAAGGAGAAGAAGATGGCTTTGGATGAGTCTGTA 1815
 |||||||
 1767 GTGGGCATGAAGCTCAAGGAGAAGAAGATGGCTTTGGATGAGTCTGTA 1816
 |||||||
 1816 CCAGTCTCAAAGACCTGAGAAGCAGAGGCAATTCTAAGGGTGGCTATGCA 1865
 |||||||
 1817 CCAGTCTCAAAGACCTGAGAAGCAGAGGCAATTCTAAGGGTGGCTATGCA 1866
 |||||||
 1866 GGAAGGAGCCAAAGAGGGGTTGCCCTCACCATCCAGGCCCTGGGAGAC 1915
 |||||||
 1867 GGAAGGAGCCAAAGAGGGGTTGCCCTCACCATCCAGGCCCTGGGAGAC 1916
 |||||||
 1916 TAGCCATGGACATACCTGGGACAAGAGTTCTACCCAAAGGGCGAATTCTG 1965
 |||||||
 1917 TAGCCATGGACATACCTGGGACAAGAGTTCTACCCACCCACCCACCCAC 1960
 |||||||
 1966 TTAAACCTGCAGGA.CTAG..... 1983
 |||||
 1961 TTAGAACTGCAGGAGCTCCCTGCTGCCTCCAGGCCAAAGCTAGAGCTTT 2010
 .
 .





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FIG. 4B

160	170	180	190	200	210
COE-2	VWFPGGAFTIVGAASSYEGSDLAAREKVVVLVFLQHRLGIFGFLSTDDSHARGNWGLLDQMA				
pro873	VWFPGGAFTIVGAASSYEGSDLAAREKVVVLVFLQHRLGIFGFLSTDDSHARGNWGLLDQMA	250	260	270	280
					290
					300
220	230	240	250	260	270
COE-2	ALRWVQENIAAFGGDPGNVTILFGQSAGAMSISGLMMSPLASGLFHRAISQSGTALFRLIFI				
pro873	ALRWVQENIAAFGGDPGNVTILFGQSAGAMSISGLMMSPLASGLFHRAISQSGTALFRLIFI	310	320	330	340
					350
					360
280	290	300	310	320	330
COE-2	TSNPLKVAKKVAHLAGCNHNSTQILVNCLRALSGTAKVIRVSNSKMRFLQLNQFQDPEEITW				
pro873	TSNPLKVAKKVAHLAGCNHNSTQILVNCLRALSGTAKVIRVSNSKMRFLQLNQFQDPEEITW	370	380	390	400
					410
					420
340	350	360	370	380	390
COE-2	SMSPVVDGVVVIPDDPLVLLTQGKVSSVPYLLGVNNLEFNWLILPYIMKFLPRLNQAMRKETI				
pro873	SMSPVVDGVVVIPDDPLVLLTQGKVSSVPYLLGVNNLEFNWLILPY	430	440	450	460
400	410	420	430	440	450
COE-2	TKMLMSTRTLINITKEQVPLVVEEYLLDNVNEHDWIKMLRNRMMDIVQDATFVYATLQTAHY				
pro873	-----NITKEQVPLVVEEYLLDNVNEHDWIKMLRNRMMDIVQDATFVYATLQTAHY	470	480	490	500
					510



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FIG. 4C

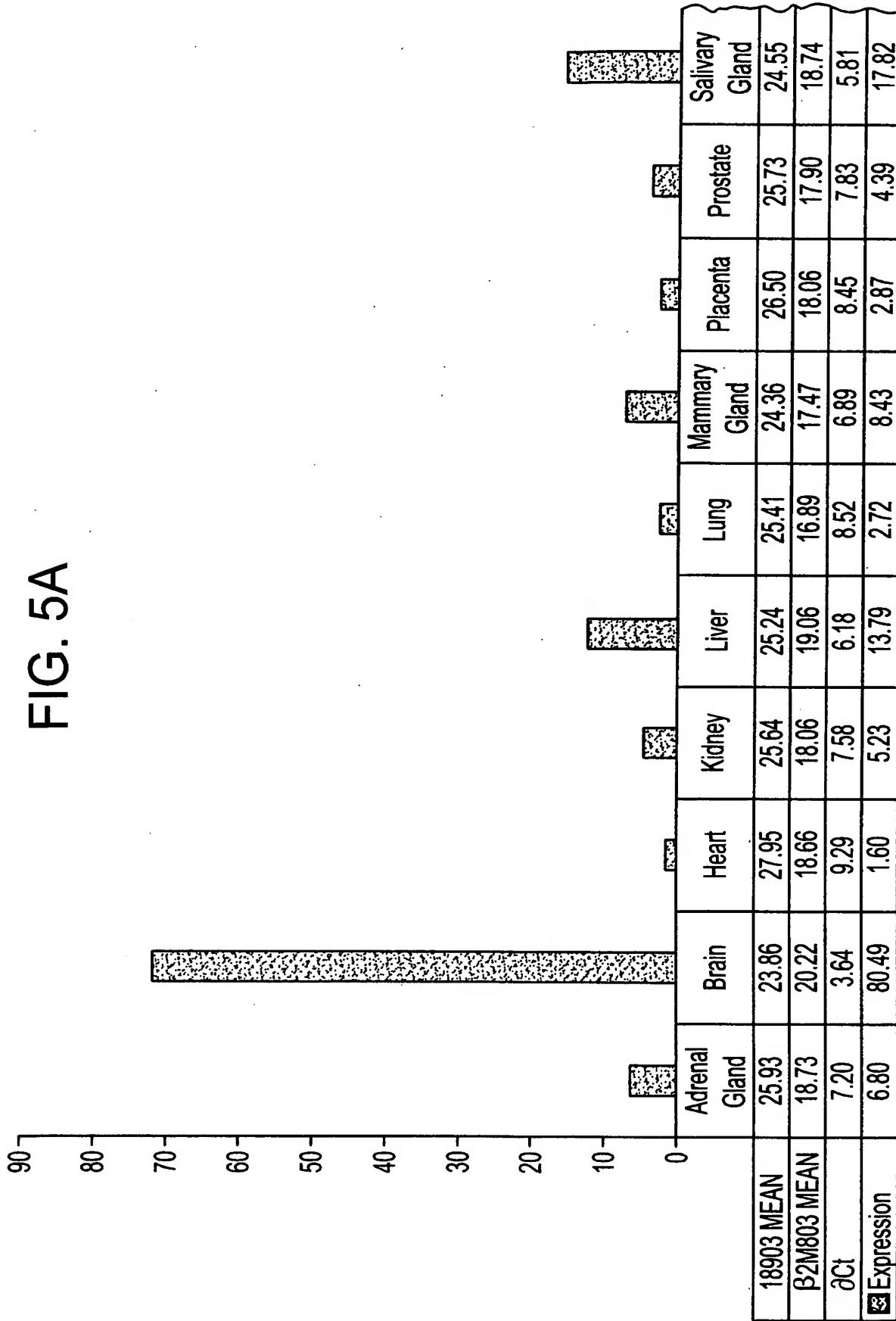
460	470	480	490	500	510
COE-2	HRDAGLGPVLYEFEHHARGIIVKPRTDGAHDGDEMVFLEFGGPATGLSSMGKEKALSLQMM				
pro873	HRET--PMM-----GIC--P---AGHA-----				
	520				
520	530	540	550	560	570
COE-2	KYWANFARTGNPNDGNLPCWPRYNKDEKYLQLDFTTRVGMKILKEKKMAFWMSLYQSQRPE				
pro873	-----TTRM-----KSTCWSIL-----P-----				
	530				
580					
COE-2	KQRQF				
pro873	-QEWA				

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FIG. 5A



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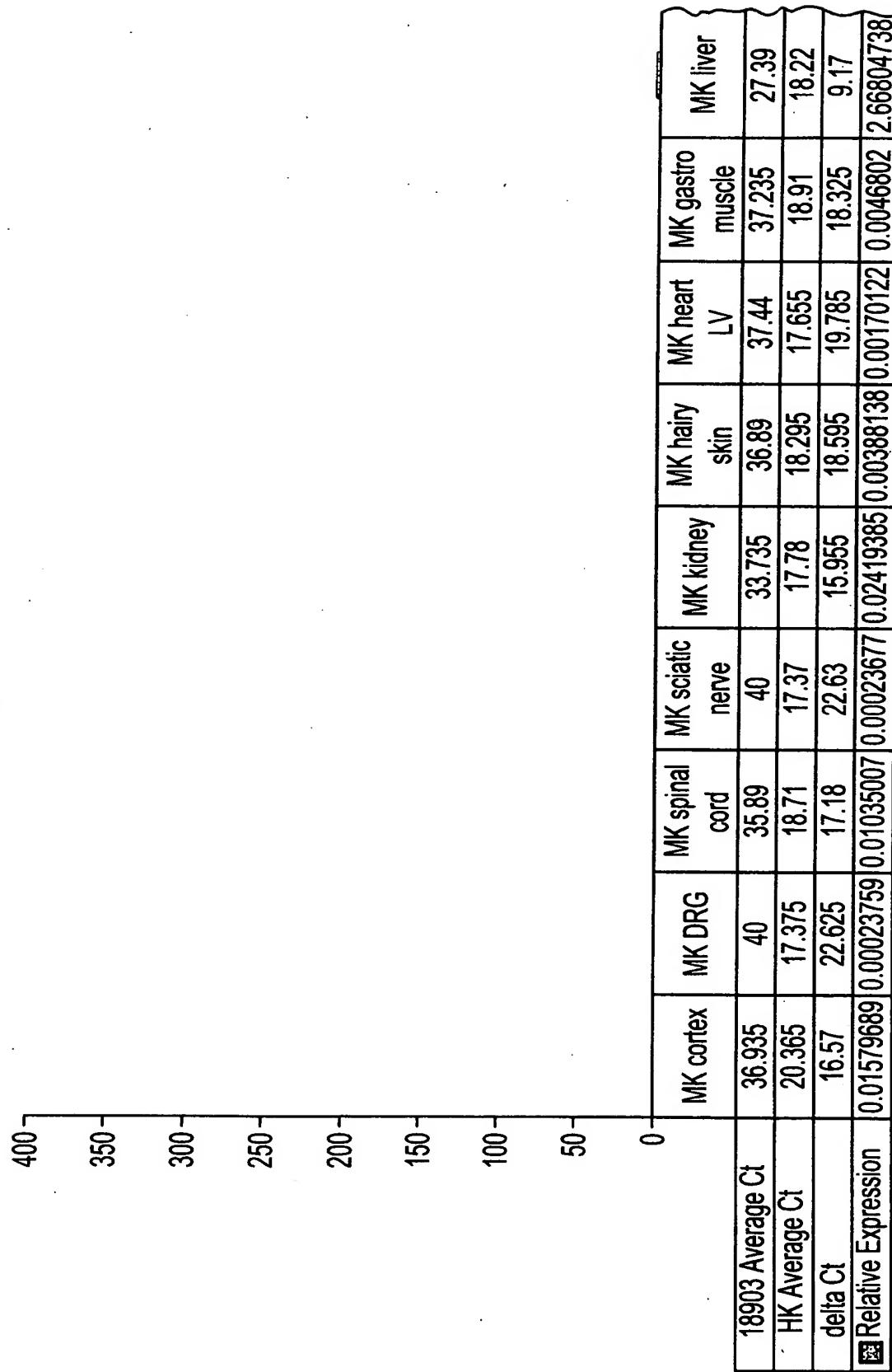
FIG. 5B

Muscle	Sm. Intestine	Spleen	Stomach	Teste	Thymus	Trachea	Uterus	Spinal Cord	Skin	DRG
29.70	25.43	26.89	26.27	24.29	26.33	25.14	26.18	23.99	23.01	25.06
20.66	17.86	16.37	18.03	19.32	18.19	19.10	18.53	19.20	17.10	19.07
9.04	7.58	10.52	8.25	4.97	8.15	6.04	7.66	4.80	5.91	5.99
1.91	5.24	0.68	3.30	31.91	3.53	15.25	4.96	36.02	16.63	15.73

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FIG. 6A





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FIG. 6B

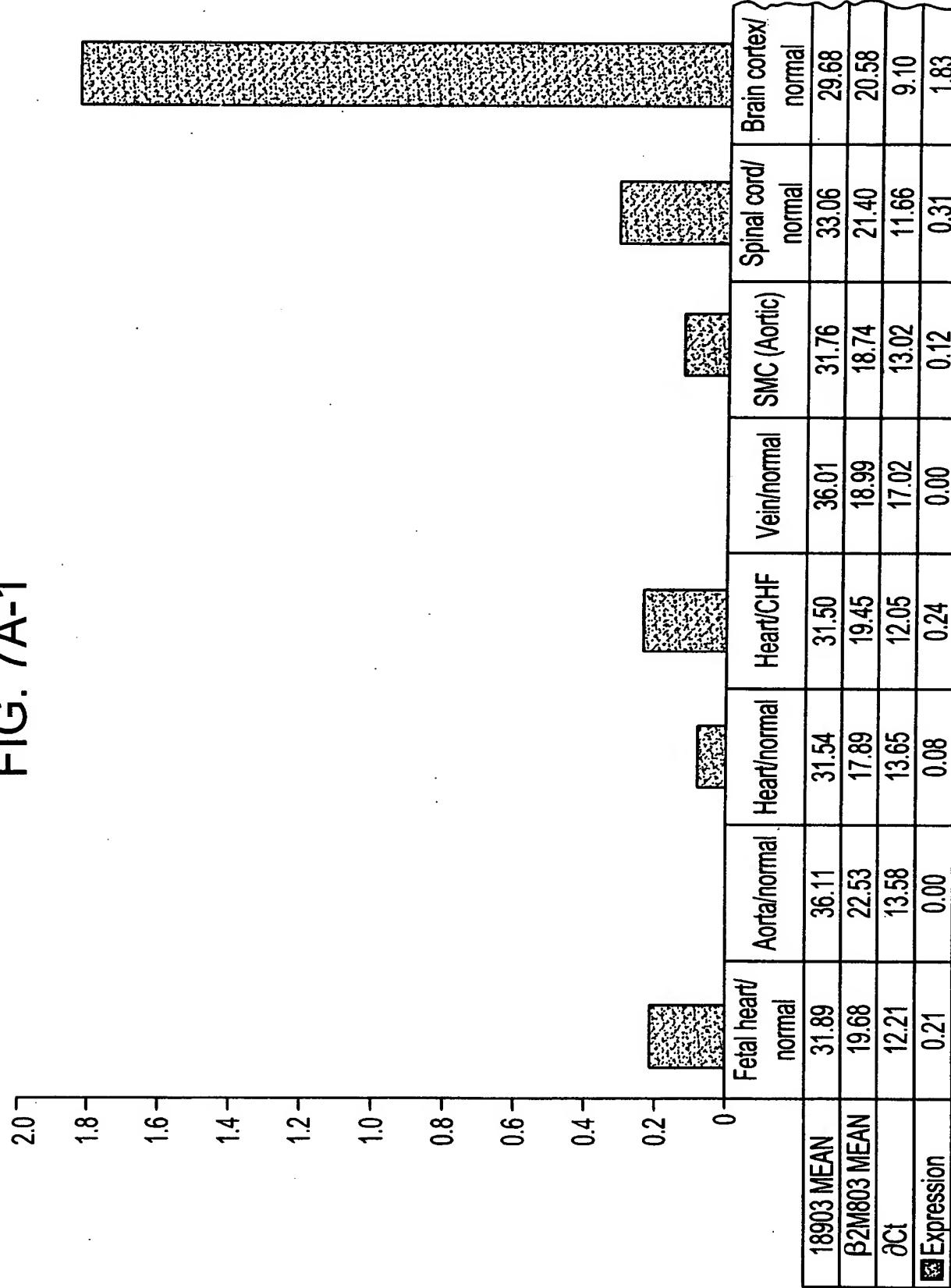
Hu. Brain	Hu. Spinal cord	Hu. Heart	Hu. Kidney	Hu. Liver	Hu. Lung
21.27	23.78	28.26	26.155	25.43	25.805
19.245	18.295	17.855	17.925	18.22	15.87
2.025	5.485	10.405	8.23	7.21	9.935
377.618146	34.3154004	1.133499992	5.11872423	10.3803579	1.57002147



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FIG. 7A-1





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FIG. 7A-2

Brain	Gliial cells (Astrocytes)	Brain/ Glioblastoma	Breast/ normal	Breast tumor/ IDC	OVARY/ Normal	OVARY/ Tumor	Pancreas	Prostate/ Normal	Prostate/ Tumor
29.45	33.94	30.39	30.10	30.75	31.73	33.59	30.88	31.16	29.03
19.24	21.09	17.43	18.60	17.66	19.95	18.91	17.33	18.34	17.57
10.21	12.86	12.97	11.50	13.09	11.79	14.68	13.55	12.83	11.46
0.85	0.13	0.13	0.35	0.11	0.28	0.04	0.08	0.14	0.35



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FIG. 7A-3

Colon/normal	Colon/tumor	Colon/IBD	Kidney/normal	Liver/normal	Liver fibrosis	Fetal Liver/normal	Lung/normal	Lung/tumor
32.03	30.80	32.37	30.98	31.82	30.10	33.55	30.54	30.30
17.78	18.15	17.72	20.03	19.08	18.82	21.39	17.31	17.77
14.26	12.66	14.65	10.95	12.75	11.29	12.16	13.23	12.53
0.05	0.16	0.04	0.51	0.15	0.40	0.22	0.10	0.17

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FIG. 7A-4

Lung/COPD	Tonsil/normal	Lymph node/normal	Thymus/normal	Epithelial Cells (Prostate)	Endothelial Cells (Aortic)	Skeletal Muscle	Fibroblasts (Dermal)	Skin/Normal	Adipose/Normal
29.44	31.13	31.40	32.80	30.70	35.27	31.06	33.10	31.16	32.43
17.10	17.19	17.91	20.03	20.13	20.16	18.26	18.18	20.29	17.96
12.34	13.94	13.49	12.78	10.57	15.11	12.81	14.92	10.87	14.47
0.19	0.06	0.09	0.14	0.66	0.03	0.14	0.03	0.54	0.04

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FIG. 7A-5

Osteoblasts (Primary)	Osteoblasts (Undiff)	Osteoblasts (Diff)	Osteoclasts	Aorta SMC (Early)	Aorta SMC (Late)	HUVEC	HMVEC
34.84	33.19	33.23	32.47	32.50	32.72	32.17	32.74
20.44	18.50	17.83	17.25	19.53	18.77	19.27	18.74
14.40	14.69	15.40	15.22	12.97	13.96	12.91	14.00
0.05	0.04	0.02	0.03	0.13	0.06	0.13	0.06



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FIG. 7B

Tissue	18903 MEAN	β 2M803 MEAN	δ	Ct	Expression
Fetal heart/normal	31.89	19.68	12.21	0.21	
Aorta/normal	36.11	22.53	13.58	0.00	
Heart normal	31.54	17.89	13.65	0.08	
Heart/CHF	31.50	19.45	12.05	0.24	
Vein/normal	36.01	18.99	17.02	0.00	
SMC (Aortic)	31.76	18.74	13.02	0.12	
Spinal cord/normal	33.06	21.40	11.66	0.31	
Brain cortex/normal	29.68	20.58	9.10	1.83	
Brain hypothalamus/normal	29.45	19.24	10.21	0.85	
Glial cells (Astrocytes)	33.94	21.09	12.86	0.13	
Brain/Glioblastoma	30.39	17.43	12.97	0.13	
Breast/normal	30.10	18.60	11.50	0.35	
Breast tumor/IDC	30.75	17.66	13.09	0.11	
Ovary/normal	31.73	19.95	11.79	0.28	
Ovary/tumor	33.59	18.91	14.68	0.04	
Pancreas	30.88	17.33	13.55	0.08	
Prostate/normal	31.16	18.34	12.83	0.14	
Prostate/tumor	29.03	17.57	11.46	0.35	
Colon/normal	32.03	17.78	14.26	0.05	
Colon/tumor	30.80	18.15	12.66	0.16	
Colon/IBD	32.37	17.72	14.65	0.04	
Kidney/normal	30.98	20.03	10.95	0.51	
Liver/normal	31.82	19.08	12.75	0.15	
Liver/fibrosis	30.10	18.82	11.29	0.40	
Fetal Liver/normal	33.55	21.39	12.16	0.22	
Lung/normal	30.54	17.31	13.23	0.10	
Lung/tumor	30.30	17.77	12.53	0.17	
Lung/COPD	29.44	17.10	12.34	0.19	
Tonsil/normal	31.13	17.19	13.94	0.06	
Lymph node/normal	31.40	17.91	13.49	0.09	
Thymus/normal	32.80	20.03	12.78	0.14	
Epithelial Cells(prostate)	30.70	20.13	10.57	0.66	
Endothelial Cells(aortic)	35.27	20.16	15.11	0.03	
Skeletal Muscle/normal	31.06	18.26	12.81	0.14	
Fibroblasts (Dermal)	33.10	18.18	14.92	0.03	
Skin/normal	31.16	20.29	10.87	0.54	
Adipose/normal	32.43	17.96	14.47	0.04	
Osteoblasts (primary)	34.84	20.44	14.40	0.05	
Osteoblasts (Undiff)	33.19	18.50	14.69	0.04	
Osteoblasts (Diff)	33.23	17.83	15.40	0.02	
Osteoblasts	32.47	17.25	15.22	0.03	
Aorta SMC (Early)	32.50	19.53	12.97	0.13	
Aorta SMC (Late)	32.72	18.77	13.96	0.06	
HUVEC	32.17	19.27	12.91	0.13	
HMVEC	32.74	18.74	14.00	0.06	
	40.00	40.00	0.00		